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EDITORIAL

Parkinson's, where are we heading?

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Abstract

The prevalence of Parkinson's disease has rapidly increased over the last decade. This editorial discusses our current understanding of the pathophysiological basis for the condition, with a particular focus on the potential role of α-synuclein, and the consequent implications this has for both the development of new investigations and disease-modifying therapies. Specifically, the article discusses the development of a new diagnostic test for cerebrospinal fluid α-synuclein, the development of a new staging system for Parkinson's disease, which takes into account the α-synuclein, genetic and neuro-imaging status, and the results of two recently completed clinical trials, using monoclonal antibodies wherein α-synuclein is the principal target. We also discuss the increasing awareness of the importance of non-motor symptoms in Parkinson's disease including hyposmia, rapid eye movement sleep behaviour disorder, and autonomic and cognitive symptoms.

Key words: α-synuclein seeding amplification assay; Neuronal α-synuclein disease; Parkinson's

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Main text

Parkinson's disease (PD) is a chronic neurodegenerative disease. In the context of a progressively ageing population worldwide, its prevalence has increased rapidly over the last few decades. This editorial aims to summarise advances in the knowledge of the pathophysiology of PD, increase awareness of non-motor and prodromal features of PD, and discuss the potential benefits of new diagnostic tests for α-synuclein and staging systems for PD. We also discuss recent clinical trials that have evaluated the effects of disease-modifying therapies for PD.

In patients with idiopathic PD, histopathological studies have demonstrated progressive neuronal loss. For most patients, there is a progressive accumulation of proteinaceous intraneuronal inclusions (Lewy bodies and Lewy neurites) in subcortical and cortical structures (Goedert et al, 2013). The major component of Lewy bodies and Lewy neurites is an aggregated form of α-synuclein, a protein that participates in regulating synaptic vesicle fusion to the plasma membrane. Abnormally misfolded α-synuclein monomers aggregate into oligomers and then fibrils. These are believed to be toxic species that lead not only to direct neuronal damage but also to spread between neurons in a prion-like manner. The causes and mechanisms that lead to α-synuclein misfolding and aggregation are currently unknown.

It has recently been proposed that the spread of α-synuclein pathology in PD could follow two different trajectories. Horsager and colleagues (2020) have used *in vivo* imaging to provide evidence for both a 'top-down' mode of propagation wherein α-synuclein pathology appears to start in the brain and subsequently spread to the peripheral autonomic nervous system (Brain-first), and a 'bottom-up' pattern of propagation-wherein α-synuclein pathology appears to start from the enteric or peripheral autonomic nervous system and then spreads to the brain (Body-first).

This dual pattern 'Brain-first, Body-first' hypothesis may go some way towards explaining why patients with PD have multiple potential presentations and why their symptoms may progress in such a varied fashion throughout the course of their disease. Individuals with PD experience a combination of motor and non-motor symptoms (NMS) that can vary from patient to patient. The classical motor symptoms, which include a rest tremor, slowness of movements (bradykinesia), and increased muscular tone (rigidity), are usually the trigger for a patient or their relatives to seek medical attention. There is variation in the presenting motor symptoms. Patients who present with a tremor-dominant phenotype,

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characterised by a dominant or isolated asymmetric rest tremor are thought to have a better prognosis, than the rarer group of patients, who present with balance and gait disturbances. The occurrence of the latter symptoms in the initial stages of the disease characterises the postural instability and gait disorders (PIGD) subtype of PD. Patients with a PIGD presentation have a more severe condition than patients with tremor-dominant disease and tend to have a faster progression, typically associated with an earlier onset of cognitive decline (Burn et al, 2006).

Non-motor symptoms of PD can occur at any stage of the disease. A patient may experience many of them, including autonomic dysfunction, hyposmia and mood disorders, years before the onset of the motor symptoms. A recent study identified that NMS was experienced by 90.3% of patients before their diagnosis of PD. NMS were rarely monosymptomatic, with patients experiencing a median of four NMS before their diagnosis (Durcan et al, 2019). Interestingly, a gender difference existed in the prodromal NMS experienced, with males reporting more sexual dysfunction, forgetfulness, and dream enactment, while females reported more unexplained weight change and anxiety. The study demonstrated a significant association between the PIGD phenotype and prodromal gastrointestinal and urinary symptoms. While many of these symptoms are non-specific and have a high prevalence in the 'healthy' ageing population, hyposmia and isolated REM (rapid eye movement) sleep behaviour disorder (iRBD) are currently considered strong risk factors for PD. Many patients with these two symptoms already have underlying α-synuclein pathology. Neuroimaging study has clearly demonstrated that many of these patients already have subclinical nigrostriatal dysfunction as measured by ^{123}I-Ioflupane SPECT (DaTSCAN) and ^{18}F-Dihydroxyphenylalanine Positron Emission Tomography (^{18}F-DOPA PET), two different markers of the integrity of striatal dopaminergic presynaptic terminals (Wasserman et al, 2021). In patients with iRBD, Positron Emission Tomography (PET) imaging has demonstrated widespread cholinergic dysfunction (Stær et al, 2024). Finally, abnormal α-synuclein has been detected in the cerebrospinal fluid (CSF) of patients with either hyposmia or iRBD (Iranzo et al, 2023) (see below), providing further evidence that these patients have an ongoing α-synucleinopathy that increases their risk of developing a parkinsonism (either PD, Multiple System Atrophy (MSA) or Dementia with Lewy Bodies) in the future.

While to date the diagnosis of PD remains based on the clinical presentation, specialised imaging, such as DaTSCAN can be performed to detect nigrostriatal dysfunction. This can support the diagnosis of neurodegenerative Parkinsonism and differentiate PD from other conditions with normal DaTSCAN such as essential tremor, dystonic tremor, and vascular parkinsonism. DaTSCAN, however, does not differentiate idiopathic PD from other causes of neurodegenerative parkinsonism such as MSA and Progressive Supranuclear Palsy. In early PD, the DaTSCAN shows an asymmetrical reduction of ligand uptake in the posterior part of the putamen with preserved caudate uptake. Bilateral caudate involvement at diagnosis appears to be associated with an increased risk of developing cognitive impairment, depression, and gait problems over the next few years (Pasquini et al, 2019).

Conventional Magnetic Resonance Imaging (MRI) sequences are typically normal in patients with idiopathic PD but can be helpful in evaluating for causes of secondary parkinsonism, such as vascular parkinsonism. Additionally, atypical Parkinsonian syndromes might show characteristic features that, if present, can support the diagnosis of these conditions. Although not in routine clinical practice, recently developed neuromelanin-sensitive MRI sequences and nigrosome imaging, mean that MRI is able to detect nigral pathology and potentially improve the diagnosis of PD (Xing et al, 2022). The clinical utility of these techniques and their generalizability are currently limited due to the lack of standardisation of acquisition protocols and analysis approaches, but it is highly likely that the extensive ongoing research in the field will be able to address these issues in the near future. This has the potential to make MRI an inexpensive and widely available tool to investigate PD in the future.

An exciting development in the field has been the development of a highly accurate biological test called the α-synuclein seeding amplification assay (αSyn-SAA). It is capable of objectively and reliably detecting the presence of abnormal α-synuclein in the CSF of people with PD (Sensitivity 93%, Specificity 94% in sporadic PD) (Siderowf et al, 2023). Furthermore, in a prodromal cohort, most individuals with hyposmia (over the age of 60)

and iRBD patients were αSyn-SAA positive. In these individuals SAA positivity appeared to precede DaTSCAN deficit.

The ability to detect clear biomarkers of α-synucleinopathy (αSyn-SAA) and neurodegeneration (DaTSCAN) in individuals at risk of PD has led to a new concept: neuronal α-synuclein disease (NSD). This moves the field away from a strict clinical definition of PD towards a wider biological definition. It applies to all those individuals who have biomarker evidence of α-synucleinopathy, not only those with motor symptoms of PD. An integrated staging system for NSD has been proposed (Simuni et al, 2024). This is an initial framework that will certainly require readjustments and discussion in the scientific community. While its application in the clinical setting is premature and inappropriate, as acknowledged by the authors of the paper, the implications in the research field are enormous, especially when designing future clinical trials aimed at preventing the development of PD in individuals at increased risk.

Finally, awareness of the ability of misfolded α-synuclein to propagate between neurons has provided the rationale for the development of pharmacological strategies that aim to reduce, or even halt the spread of α-synuclein pathology throughout the central nervous system. Recently, two monoclonal antibodies targeting aggregated α-synuclein have been evaluated in clinical trials of untreated PD patients. The first agent assessed, cinpanemab, developed by Biogen, showed a similar effect on disease progression as the placebo (Lang et al, 2022). Its development was subsequently discontinued. The second agent, prasinezumab, developed by Hoffmann-La Roche also failed to meet its primary endpoint (Pagano et al, 2022). However, at the end of the double-blind phase, compared to the placebo arm, patients on prasinezumab had better motor scores as measured by the motor part of the Movement Disorder Society-Unified PD Rating Scale. Promisingly, an exploratory post hoc analysis demonstrated that prasinezumab might reduce motor progression to a greater extent in individuals with a more rapidly progressive PD (Pagano et al, 2024). A phase 2b study is currently ongoing to test the effect of prasinezumab on slowing motor progression in early-stage PD populations on stable treatment [PADOVA (NCT04777331)].

In conclusion, significant progress in our understanding of PD has been made over the last two decades. The development of a CSF test for α-synuclein, and an NSD staging system has the potential to further increase our understanding of the pathophysiology of PD and facilitate the development of new medications for the condition. Recent trials of disease-modifying treatments have shown promising preliminary results, and several agents are currently being assessed in further trials, the results of which should be available soon.

Key points

- Most patients with idiopathic PD, have histopathological evidence of intraneuronal inclusions, consisting of an aggregated form of α-synuclein. Abnormally folded α-synuclein oligomers are believed to be a toxic species that lead to direct neuronal damage and spread between neurons in a prion-like manner.
- A recently validated laboratory test, the αSyn-SAA, performed on cerebrospinal fluid, has a sensitivity of 93% and specificity of 94% in sporadic PD.
- The αSyn-SAA is often also positive in patients considered at elevated risk of developing PD, i.e., those with hyposmia or iRBD.
- This has led to proposals for a biological definition of PD, based on results of αSyn-SAA, alongside clinical, genetic and neuro-imaging features. One prominent group have proposed a new concept: NSD, wherein patients who do not currently have clinical motor signs of PD but are at high risk of developing the disorder are also included in an NSD continuum. This has important implications for future research and commercial clinical trials in PD.
- Two clinical trials, using monoclonal antibodies with an α-synuclein target, have recently been completed. Whilst their primary outcomes were not met, there was a sufficient improvement in important secondary outcomes including motor assessments (such as tremor, gait, bradykinesia, and rigidity) to warrant further investigation of these products.

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Availability of data and materials

All the data of this study are included in this article.

Author contributions

NP and DL made substantial contributions to the conception and design of this research. NP and DL drafted and wrote the manuscript. Both authors contributed to important editorial changes of important content in the manuscript. Both authors read and approved the final manuscript. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate

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Conflict of interest

The authors declare no conflict of interest.

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